PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
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REGISTERED MAIL

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

	Date of mailing *(day/month/year)* 12/01/2004
Applicant's or agent's file reference U30056PCT	**PAYMENT DUE** within 30 ~~months~~/days from the above date of mailing
International application No. PCT/EP 03/08495	International filing date *(day/month/year)* 31/07/2003
Applicant CHARITE-UNIVERSITÄTSMEDIZIN BERLIN	

1. This International Searching Authority

(i) considers that there are 7 *(number of)* inventions claimed in the international application covered by the claims indicated ~~below~~/on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~/on the extra sheet:

(ii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

1-10, 13-24 (PART)

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited,** within the time limit indicated above, to pay the amount indicated below:

EUR 945,00	x	6	=	EUR 5.670,00
Fee per additional invention		number of additional inventions		total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. [X] Claim(s) Nos. see annex _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sandrine Polenzani

Form PCT/ISA/206 (July 1992)

Important Information

general

- the **claims cannot be changed** at this point in the procedure, the transmitted report is **not** the ISR (see PCT Art. 19)
- non-payment does not lead to a **loss of rights**, a new procedure will be started on entry into the regional or national phase
- any payments have to be effected **directly** to this ISA (account details on separate sheets), payments to other entities will not be accepted
- in case of a **total of more than 2 inventions** found: when paying please **specify exactly** which claims should be searched
- an **extension of** the set **time limit** may be granted, however, the total number of days **shall not exceed 45 days** (PCT Rule 40.3). It has to be requested in writing (preferably faxed) and must be received by this ISA within the first time limit, i.e. 30 days calculating from the date of mailing.

payment by cheque or money transfer:

- the **date of payment** is considered to be the **date the money is booked** in the EPO account
- faxed cheques are not considered to be a valid payment
- only payments in EUR are accepted, no equivalents in other currencies
- payments by **credit card** are **not possible**

payment by deposit account:

- the **date of payment** is considered to be the date that the **authorisation** to deduct fees from the deposit account is **received at the EPO**

payments under protest according to Rule 40 PCT:

- the protest will **not be accepted without a payment** of additional search fee(s)
- the protest has to be **accompanied by a technical reasoning**
- no **protest fee** needs to be paid yet, only additional **search fee(s)**

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/EP 03/08495

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ✓	WO 01 47540 A (BETH ISRAEL HOSPITAL) 5 July 2001 (2001-07-05) *cf. abstract, page 7, lines 19-25, page 8, line 23 bridging with page 9, line 24, experiment 2 on pp. 46/47, claims 1/4/5* ---	1-10, 13-24
X ✓	WO 99 09006 A (BEHNKE MARK ;ROUSH WILLIAM (US); PLAMONDON LOUIS (US); SOUCY FRANC) 25 February 1999 (1999-02-25) *cf. abstract, page 9, line 15 bridging with page 10, line 2, page 31, line 2, page 41, lines 3-9, example 15 on page 67ff., page 69, lines 1-5, claims 71/72* -----	1-10, 13-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Form PCT/ISA/206 (Annex, first sheet) (July 1992)

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/EP 03/08495

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10, 13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

a) naturally occurring proteasome inhibitors comprising peptide derivatives which have a C-terminal epoxy keton structure, beta-lacton-derivatives, aclacinomycin A, lactacystin, clastolactacystin.

2. Claims: 1-10, 13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

b) synthetic proteasome inhibitors comprising: modified peptide aldehydes such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (MG132), or the boric acid derivative of MG232, N-carbobenzoxy-Leu-Nva-H (MG115), N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (LLnL), N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (PS1).

3. Claims: 1-10,13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

c) peptides comprising: an alpha,beta-epoxyketone-structure, vinyl-sulfones such as carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon or 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS).

4. Claims: 1-10, 13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

d) Glyoxal- or boric acid residues such as pyrazyl-CONH(CHPhe)CONH(CHisobutyl)B(OH)2 and dipeptidyl-boric-acid derivatives.

5. Claims: 1-10,13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

e) Pinacol-esters such as: benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacolester.

6. Claims: 11,25 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

f) a proteasome inhibitor interfering with proteasomal gene expression, selected from a group comprising antisense RNA, double stranded RNA and oligonucleotides hybridising with a DNA sequence encoding at least one component of the proteasome complex.

7. Claims: 12,26 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

g) a proteasome inhibitor interfering with a proteasomal gene expression selected from a group comprising a knock out construct

The present application concerns different groups (a-g) of proteasome inhibitors for the prevention/onset therapy/acute therapy and/or regression of "diseases associated with endothelial dysfunction", comprising ischemic diseases of organs.

However, compositions comprising proteasome inhibiting agents in the treatment of ischemic disorders including myocardial infarction or myocardial ischemia are disclosed in WO-A-01/47540 and WO-A-99/09006.

Hence the subjects as defined above are no longer linked by a common concept involving a particular technical feature pursuant to Rule 13.1 PCT. Hence the present application lacks unity of à posteriori.

Each of the above listed inventions has to be regarded as a distinct invention, characterised by its own particular technical contribution which as a whole, forms part of the prior art.

As searching the other subjects would have caused a major additional searching effort, only the first invention has been searched.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Claims Nos.: 1-2

Present claims 1-26 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear namely those compounds recited in the examples and closely related homologous compounds mentioned in the claims 6 and 7. Moreover, the claims covering all compounds having the characteristic or property of being useful in the treatment/therapy of "diseases associated with endothelial dysfunction" only find support within the meaning of Article 6 PCT within the meaning of Article 5 PCT for only a very limited number of such compounds (MG132). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent Family Annex

Information on patent family members

Interna[redacted] Application No
PCT/EP 03/08495

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0147540 A	05-07-2001	AU 2599001 A	09-07-2001
		CA 2397955 A1	05-07-2001
		EP 1242107 A1	25-09-2002
		WO 0147540 A1	05-07-2001
WO 9909006 A	25-02-1999	AU 749857 B2	04-07-2002
		AU 8906298 A	08-03-1999
		BR 9811304 A	13-11-2001
		CA 2301054 A1	25-02-1999
		CN 1271342 T	25-10-2000
		EP 1021407 A1	26-07-2000
		HU 0002724 A2	28-02-2001
		JP 2001515064 T	18-09-2001
		NZ 503169 A	21-12-2001
		WO 9909006 A1	25-02-1999
		US 6133308 A	17-10-2000
		US 2003191322 A1	09-10-2003
		US 6294560 B1	25-09-2001
		US 2002016355 A1	07-02-2002